

Flame Retardant Alternatives

Tris(1,3-dichloro-2-propyl) Phosphate

Hazard Review

Tris(1,3-dichloro-2-propyl) phosphate:
Existing Data Summary Table – Human Health Endpoints

✓ = Endpoint characterized by existing data * = Data available but not adequate ✗ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing studies. It does not indicate a positive or negative result for that particular endpoint.

<i>Acute Toxicity</i>	
Oral	✓
Dermal	✓
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	✓
<i>Subchronic Toxicity</i>	
28-Day oral	
90-Day oral	*
Combined repeated dose with reproduction/developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
<i>Reproductive Toxicity</i>	
Reproduction/developmental toxicity screen	
Combined repeated dose with reproduction/developmental toxicity screen	
Reproduction and fertility effects	*

<i>Developmental Toxicity</i>	
Reproduction/developmental toxicity screen	
Combined repeated dose with reproduction/developmental toxicity screen	
Prenatal developmental	✓
<i>Chronic Toxicity</i>	
Chronic toxicity (two species)	
Combined chronic toxicity/carcinogenicity	✓
<i>Carcinogenicity</i>	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/carcinogenicity	✓

<i>Neurotoxicity</i>	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	*
Additional neurotoxicity studies	✗
<i>Immunotoxicity</i>	
Immunotoxicity	*
<i>Genotoxicity</i>	
Gene mutation in vitro	✓
Gene mutation in vivo	✓
Chromosomal aberrations in vitro	✓
Chromosomal aberrations in vivo	*
DNA damage and repair	✓
Other	

Tris(1,3-dichloro-2-propyl) phosphate:
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓ = Endpoint characterized by existing data * = Data available but not adequate ✗ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	✓
Octanol/water partition coefficient	✓
Oxidation/reduction	
Melting point	✓
Boiling point	✓
Vapor pressure	*
Odor	✓
Oxidation/reduction chemical incompatibility	
Flammability	✓
Explosivity	
Corrosion characteristics	
pH	✗
UV/visible absorption	✓
Viscosity	✓
Density/relative density/bulk density	✓
Dissociation constant in water	✗
Henry's Law constant	

Environmental Fate	
<i>Bioconcentration</i>	
Fish	✓
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	*
<i>Degradation and Transport</i>	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	✓
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	*
Hydrolysis as a function of pH	✓
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
<i>Aquatic Toxicity</i>	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	*
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
<i>Terrestrial Organism Toxicity</i>	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	*

Chemical Identity

2-Propanol, 1,3-dichloro-, phosphate (3:1)

CAS 13674-87-8

MF $C_9H_{15}Cl_6O_4P$

MW 430.91

SMILES ClCC(CCl)OP(=O)(OC(CCl)CCl)OC(CCl)CCl

Synonyms Tris(1,3-dichloro-2-propyl) phosphate, TDCPP, Fyrol FR-2

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute oral lethality studies were available in a variety of species: rabbits, rats, and mice. These studies were from the older (pre 1980) literature, did not report substance purity, and do not fully conform to OPPTS or OECD guidelines, but given the magnitude of the LD50 values the data are adequate for the evaluation of acute oral toxicity. Acute oral LD50 values generally exceeded the current limit dose of 2,000 mg/kg. Reports that specified a 14-day observation period are presented in detail.

Critical Studies:

Type: Acute oral toxicity

Species, strain, sex, number: Rabbit, Dutch-belted, 5 males/group

Doses: 0, 5,000, 7,500, and 10,000 mg/kg

Purity: Fyrol FR-2; purity not specifically reported

Vehicle: Not reported by Akzo-Nobel

Method: 14-Day post-dosing observation period; observations limited to mortality, clinical signs, and necropsy. LD50 calculated according to Litchfield and Wilcoxon.

Results: Clinical signs shortly after dosing included ataxia, weakness, and diarrhea; survivors normal by day 9. Necropsy revealed no abnormalities. Acute oral male rabbit LD50 = 6,800 mg/kg (95% CI 5,615-8,234 mg/kg).

Reference: Robust summary from Akzo-Nobel, 2001a, unpublished study conducted 1982

Type: Acute oral toxicity

Species, strain, sex, number: Rat, Sprague-Dawley, 5 males/group

Dose: 1,000, 2,150, 5,640, or 10,000 mg/kg

Purity: Fyrol FR-2; purity not specifically reported

Vehicle: None

Observation period: 14 days post dosing

Method: 14-Day post-dosing observation period; observations limited to mortality, clinical signs, and necropsy; LD50 calculated according to Litchfield and Wilcoxon; not specified whether fed or fasted at time of dosing.

Results: No effects at 1,000 mg/kg. Dose-related depression at or above 2,160 mg/kg; survivors normal by day 5. No gross lesions in survivors; fatalities had congestion of heart, lung, and liver. Acute rat oral LD50 = 3,160 mg/kg (95% CI 2,050-4,800 mg/kg)

Reference: Stauffer, 1972d; robust summary from Akzo-Nobel, 2001a

Type: Acute oral toxicity

Species, strain, sex, number: Mouse, Slc/ddY, 10/sex/dose

Purity: Not reported

Doses: For males: 0, 2,210, 2,380, 2,570, 2,780, 3,000, 3,240, and 3,500 mg/kg. For females: 0, 2,890, 2,040, 2,210, 2,380, 2,570, and 2,780 mg/kg.

Vehicle: Olive oil

Method: Observed for mortality and clinical signs for 14 days. No body weight or gross necropsy examination.

Results: Treated animals exhibited ataxic gait, hyperactivity, convulsion and death. No mortality was observed in controls or in males at 2,210 mg/kg or females at 1,890 mg/kg. The LD50 values were 2,670 mg/kg (2,520-2,830 mg/kg) for male mice and 2,250 (2,120-2,380 mg/kg) for female mice.

Reference: Kamata et al., 1989

Additional Studies and Information:

Other studies available only in secondary sources reported similar results. An oral LD50 of >2,000 mg/kg was reported in male and female rats exposed to Tolgard TDCP MK1 (Cuthbert, 1989a as reported in WHO, 1998); clinical signs observed during the first 5 days after dosing included hypokinesia, piloerection, soiled coats, ataxia, chromodacryorrhea, rhinorrhea, and salivation.

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available studies predate the preferred study guidelines, and did not report purity, but together indicated no mortality at the guideline limit dose of 2,000 mg/kg. The report specifying a 14-day observation period is presented in more detail.

Type: Acute dermal toxicity

Species, strain, sex, number: Rabbit, New Zealand albino, sex not specified, 4

Dose: 4,640 mg/kg

Purity: Fyrol FR-2; Stauffer, no data

Vehicle: None

Exposure period: 24 Hour

Method: 4 Rabbits tested occluded; 14-day observation period. Gross necropsy.

Results: Mortality after 14 days = 0/4. No overt signs of toxicity and no gross necropsy findings. Therefore, dermal acute LD50 >4,640 mg/kg.

Reference: Stauffer, 1973a; additional information from robust summary in Akzo-Nobel, 2001a

Additional Studies and Information:

Other studies available only in secondary sources with minimal detail. A dermal LD50 of >2,000 mg/kg was reported in male and female Sprague-Dawley rats exposed to Tolgard TDCP MK1 (Cuthbert, 1989b as reported in WHO, 1998). No deaths and no clinical signs were noted 24 hours after treatment.

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available study on TDCPP predates the preferred guidelines. The duration was shorter than currently recommended and no deaths were observed. Analysis of aerosol particle size, however, was not mentioned so it is not known whether the size was respirable. Necropsies were not performed.

Type: Acute inhalation toxicity

Species, strain, sex, number: Rat, Sprague-Dawley, 5 males and 5 females

Doses: 9.8 mg/L (9,800 mg/m³)

Purity: No data

Vehicle: None

Duration: 1 hour

Method: Observation period = 14 days. Observed daily for signs of toxicity and for mortality.

Results: No mortality after 14 days; initial signs of moderate depression

Reference: Stauffer, 1973b

Additional Studies and Information:

Other studies available only in secondary sources reported similar results. An acute inhalation LC50 of $>5,220 \text{ mg/m}^3$ was reported for Sprague-Dawley rats exposed to aerosol of TDCPP (Amgard TDCP) (Anderson, 1990 as reported in WHO, 1998).

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies report similar results in rabbits: mild reversible irritation of the conjunctiva. The studies are summarized below.

Type: Acute eye irritation

Species, strain, sex, number: Rabbit, New Zealand White, sex not specified; 6

Doses: 0.1 mL

Purity: No data, Stauffer Fyrol FR-2

Vehicle: None

Method: Cited CFR [U.S. Federal Hazardous Substances Labelling Act] Section 191.12, chapter 1, title 21. Following instillation of TDCPP, eyes were examined at 24, 48, and 72 hours.

Results: Mild conjunctival effects in 3/6 that cleared by 48 hours.

Reference: Stauffer, 1972c

Type: Acute (24-hour) eye irritation

Species, strain, sex, number: Rabbit, New Zealand White, male and female; 9 total

Doses: 0.1 mL

Purity: No data

Vehicle: None

Method: U.S. EPA Hazard Evaluation. 1978. Fed. Reg. 43: 163: pp. 37331-37402. Thirty seconds following instillation of TDCPP, the treated eyes of three rabbits were washed, treated eyes were not washed in 6 rabbits. The untreated eye of each animal served as a control. The cornea, iris and conjunctiva of each eye were examined at 24, 48, and 72 hours, and at 4 and 7 days after instillation of TDCPP using the Draize scoring method.

Results: No signs of eye irritation were observed (average total Draize score of zero).

Reference: Stauffer, 1979; robust summary from Akzo-Nobel, 2001a for study dated 1979

Additional Studies and Information:

One hour following application of Tolgard TDCP MK1 to the eyes of New Zealand White rabbits, slight conjunctival redness and slight discharge were noted (Cuthbert and Jackson, 1990 as reported in WHO, 1998); effects cleared by 24 hours.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies, patterned after guidelines in effect at the time, provide similar results, indicating that TDCPP was a non-irritant when applied for 4 hours (consistent with current guidelines) and a mild irritant when applied for 24 hours to rabbit skin. Additional studies provide support. The studies are summarized below.

Critical Studies:

Type: Acute (24-hour) dermal irritation

Species, strain, sex, number: Rabbit, New Zealand, sex not specified, 6

Doses: 0.5 mL

Purity: Not reported; Stauffer Fyrol FR-2

Vehicle: None

Method: Cites "EPA protocol". Back hair was shaved, each rabbit tested on intact and abraded skin, occlusive dressing removed after 24 hours, observations at 24 and 72 hours.

Results: No edema on intact or abraded skin in any of the 6 rabbits. Mild erythema was visible at 24 hours but cleared by 72 hours, resulting in a score of 0.63. The report classified TDCPP as a mild irritant.

Reference: Stauffer, 1979

Type: Acute (4-hour) dermal irritation

Species, strain, sex, number: Rabbit, not specified (but New Zealand white rabbits were used in an eye irritation test conducted at the same time)

Doses: 0.5 mL

Purity: Not reported; Stauffer Fyrol FR-2

Vehicle: None

Method: Back hair shaved, each rabbit tested on intact and abraded skin, occlusive dressing removed after 4 hours, observations at 4, 24 and 48 hours.

Results: No erythema or edema on intact or abraded skin in any of the 6 rabbits.

Reference: Stauffer, 1972c

Additional Studies:

Another study, on Tolgard TDCPP MK1, reported well-defined (score 2) erythema in 2 New Zealand White rabbits and slight erythema in a third rabbit 1 hour after patch removal, but duration of exposure was not specified (Cuthbert, 1989c as reported in WHO, 1998). Effects cleared by 48 hours. The substance was classified as a skin irritant.

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

Conclusion:

The available skin sensitization data were judged adequate to meet the endpoint.

Basis for Conclusion:

A confidential study that reported negative results in a skin sensitization study in guinea pigs was submitted that allows this endpoint to be adequately characterized.

A robust summary in a submission to the HPV Challenge program was located for an unpublished industrial study stated to have been conducted under guideline. The summary probably has not been reviewed by EPA, since this endpoint is not required for the HPV program. Furthermore, the summary omits information necessary to determine study adequacy, such as: the strain, sex, group size, substance purity, and dose levels. The summary claimed that the doses were selected according to guideline, but the exact levels are not stipulated in the guideline. Without the additional information, this study cannot be evaluated for adequacy.

Critical Studies:

Type: Dermal sensitization study

Species, strain, sex, number: Guinea pig, strain and sex not reported

Doses: Stated as according to guideline, but exact doses are not stipulated in guideline.

Purity: Not reported; Fyrol FR-2

Vehicle: Water

Method: Three pairs of intradermal injections into shaved shoulder: 1:1 Freund's Complete Adjuvant (FCA) and saline, the test material, and 1:1 FCA and test material. Controls received water in place of the test material. On day 6, 24 hours before topical induction application, sodium lauryl sulfate was applied to sites to enhance local irritation. On day 7, test substance was applied to sites (water for controls). On day 21, animals received challenge dose by dermal application, occluded for 24 hours. Sites observed for irritation and sensitization (Grade 0-4).

Results: The sensitization score for Fyrol FR-2 was zero, indicating the substance is not a chemical sensitizer.

Reference: Robust summary in Akzo-Nobel, 2001b for unpublished and unidentified study dated 2001

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A Japanese 90-day dietary study in mice (Kamata et al. 1989) provides limited relevant information in the English abstract and data tables. The study was not adequate to characterize this endpoint because histopathological analysis was apparently limited to the liver. A fertility study by Wilczynski et al. (1983), discussed under the Reproductive Toxicity endpoint, evaluated male rabbits exposed by oral gavage for 12 weeks, but did not involve treated females.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

No study of this type was located.

90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)

Type: 90-Day repeated oral

Species, strain, sex, number: Mouse, Slc/ddY, 12/sex/dose

Doses: TDCPP at dietary concentrations of 0, 0.01, 0.04, 0.13, 0.42, and 1.33% in the diet, resulting in reported average daily doses of 0, 13.2, 47.3, 171.0, 576.0, and 1,792.3 mg/kg/day in males and 0, 15.3, 62.5, 213.6, 598.0, and 1,973.1 mg/kg/day in female mice

Purity: Not reported

Vehicle: None; added to diet

Exposure period, frequency: 90 days, ad lib

Method: Body weight, food consumption measured weekly. At 1 and 3 months in half the animals, hematologic (erythrocyte, hemoglobin, hematocrit, and leukocyte counts) and clinical chemistry parameters (total protein, albumin, albumin/globulin ratio, blood urea nitrogen, glucose, total cholesterol, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase). At 1 and 3 months, half the animals were necropsied and absolute and relative organ weights were determined for brain, heart, lung, liver, kidney, and spleen. The liver was examined for microscopic histopathology; the English text does not mention whether other tissues were examined.

Results: At the highest dietary level, 1.33%, all mice exhibited emaciation, rough hair, and tremor and died within 1 month. At 1.33%, food consumption was reduced and body weight loss occurred in both sexes. Mean body weight gain was reduced by about 10% (estimated from graph) in males at 0.42% throughout the study. The following statistically significant changes

occurred in treated groups compared to controls. Slight anemia (reduced hemoglobin; $p < 0.05$) in males at 0.42% after 3 months. Anemia (reduced hemoglobin at $\geq 0.13\%$ after 1 month and at 0.42% at 3 months, erythrocyte and hematocrit at 0.42% at 1 and 3 months) in females (3-month values $p < 0.01$). Albumin/globulin ratios elevated in all treated male groups at 3 months. Alkaline phosphatase elevated in females at 0.42% at 1 month but not later. Dose-related organ weight elevations compared to controls observed at 3 months in males included relative liver weight (+32-51%) at $\geq 0.13\%$ and relative kidney weight (+39%) at 0.42%. Significant elevations in organ weights in females at 3 months included relative liver weight (+16-51%) at $\geq 0.04\%$, absolute (+30%) and relative (+34-40%) kidney weights at $\geq 0.13\%$, and absolute liver weight (+40%) at 0.42%. The statistical significance of these organ weight elevations was $p < 0.01$ for rats exposed at $\geq 0.13\%$ and $p < 0.05$ for rats exposed at 0.04%. Histopathology of the liver (slight focal necrosis) was observed in only two females at 0.42%. The dietary level of 0.01% is a NOAEL of 15.3 mg/kg/day and the dietary level of 0.04% is a LOAEL of 62.5 mg/kg/day for liver and kidney weight elevations in female mice.

Reference: Kamata et al., 1989

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies of this type were located.

Subchronic Dermal Toxicity (21/28-day or 90-day)

Conclusion:

No available subchronic dermal toxicity data.

Basis for Conclusion:

No data exist for the subchronic dermal toxicity endpoint.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410))**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

No studies of either type were located.

Subchronic Inhalation Toxicity (90-day)

Conclusion:

No available subchronic inhalation toxicity data.

Basis for Conclusion:

No repeated-exposure inhalation toxicity studies were located.

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

No studies of this type were located.

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A fertility assay in male rabbits exposed by oral gavage for 12 weeks prior to mating (Wilczynski et al., 1983) partially characterizes this endpoint, but is not sufficient to satisfy the reproductive toxicity endpoint since it was described only in an abstract and females were not tested. Other studies (Hazleton, 1978; Tanaka et al., 1981) described below under Developmental Toxicity reported that in pregnant female rats exposed orally to TDCPP, adverse reproductive effects occurred only at maternally lethal doses. However, no study evaluated reproductive function in females treated prior to mating.

The 2-year feeding bioassay in rats by Freudenthal and Henrich (2000; Bio/Dynamics, 1980, 1981), discussed below under Chronic Toxicity, provides reproductive histopathology data that are, however, insufficient to satisfy the reproductive toxicity endpoint. This study provided histopathology results for the testis, epididymis, seminal vesicle, ovary, and uterus for the control and high-dose groups (0 and 80 mg/kg/day) after 1 year (10 scheduled sacrifices/sex/group) and for survivors in all groups after 2 years; unscheduled sacrifices (rats killed in a moribund state) were also examined. The 2-year exposure is too long to represent reproductive toxicity, because of the confounding effects of aging; the results pointed to dose-related effects in male reproductive organs (at ≥ 5 mg/kg/day, atrophy and decreased secretory product of the seminal vesicles; at ≥ 20 mg/kg/day, testicular germinal atrophy with oligospermia; and at 80 mg/kg/day, oligospermia and luminal accumulation of degenerated seminal products in the epididymis). No significant effect was observed in females. The tested doses, which were considerably lower than the guideline limit dose of 1,000 mg/kg/day, were not

high enough to induce significant reproductive histopathology after one year of exposure; 1/10 high-dose males had oligospermia. Thus, a LOAEL for reproductive effects following subchronic (90-day) exposure is not available and cannot be extrapolated from the existing data, but the chronic data indicate a LOAEL of 5 mg/kg/day for atrophy and decreased secretory product of the seminal vesicles.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

No studies were available that met the specific designs of the three protocols listed above.

Additional Studies:

A study described in an abstract by Wilczynski et al. (1983) addresses fertility in male rabbits exposed by oral gavage for 12 weeks prior to mating.

Type: Fertility

Species, strain, sex, number: Rabbit, strain not specified, 10 males/dose

Purity: Not reported

Doses: 0, 2, 20, or 200 mg/kg/day

Vehicle: Not reported

Exposure duration, frequency: 12 weeks, once by oral gavage daily

Method: Males treated for 12 weeks, then mated with untreated females. Body weight, clinical signs, clinical chemistry, hematology, mating behavior, male fertility, sperm quantity and quality, kidney and liver weights, gross and microscopic pathology (range of organs examined not specified).

Results: High-dose animals had significantly increased absolute kidney weight and relative liver weight. TDCPP had no effect on male reproductive parameters; there was no histopathology in kidneys, liver, pituitaries, testes, or epididymides.

Reference: Wilczynski et al., 1983

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Developmental toxicity studies in two strains of rats exposed to Fyrol FR-2 by oral gavage followed methods consistent with OECD Guideline 414 (one study pre-dated the guideline).

Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)

Type: Prenatal developmental toxicity

Species, strain, sex, number: Rat, Wistar, 15 pregnant females at the highest dose, 23-24 pregnant females in controls and other dose groups.

Purity: not reported

Doses: 0, 25, 50, 100, 200, and 400 mg/kg/day

Vehicle: Olive oil

Exposure duration, frequency: Once by oral gavage daily on gestational days (GD) 7-19.

Method: Body weight, food consumption, clinical signs, pregnancy rates, and necropsy of dams, kidney weight; uterine contents (including implants and resorption) at day 20 of gestation, corpora lutea; fetal viability, sex ratio and weight, crown-rump length, and external and skeletal abnormalities.

Seven dams from each of the control and ≤ 200 mg/kg/day groups were permitted to litter normally and evaluated for implantation sites, delivery index, number of live offspring at birth and survival on PND 4, at 4th week, and at 10th week. Litters were culled to 10 offspring on postnatal day 4 (PND 4) and subjected to behavioral tests (open field, water maze, rota rod, inclined screen, pain reflex and Preyer's reflex). Absolute organ weights of 10 organs plus testis, uterus and ovary were measured in offspring.

Results: Maternal mortality occurred only at 400 mg/kg/day: 11/15 died. Food consumption was suppressed at 400 mg/kg/day and slightly at 200 mg/kg/day. At 400 mg/kg/day, mean body weight loss occurred during GD 7-15, resulting in significantly ($p < 0.05$) reduced terminal body weight on GD20: ~17% lower than control group. Absolute and relative kidney weights were significantly increased at 200 and 400 mg/kg/day. TDCPP at ≤ 200 mg/kg/day had no effect on corpora lutea or mean numbers of implants, fetal body weight, fetal sex ratio, or the number of dead or live fetuses. The numbers of dead fetuses and live fetuses were significantly ($p < 0.01$) changed compared to controls by the loss of one whole litter at 400 mg/kg/day. No increase in malformations was observed in treated groups. For maternal toxicity, the NOAEL was 100 mg/kg/day and the LOAEL was 200 mg/kg/day for increased kidney weight. For fetal toxicity, the NOAEL was 200 mg/kg/day and the LOAEL was 400 mg/kg/day for increased fetal death; the highest dose of 400 mg/kg/day was a NOAEL for teratogenicity.

Postnatal observations: TDCPP at ≤ 200 mg/kg/day had no effect on implantation, delivery, postnatal survival, behavior, functional test results, or absolute organ weights of offspring.

Reference: Tanaka et al., 1981

Type: Prenatal developmental toxicity

Species, strain, sex, number: Rat, Sprague-Dawley, 20 pregnant females/dose

Purity: not reported

Doses: 0, 25, 100, and 400 mg/kg/day

Vehicle: Corn oil

Exposure duration, frequency: Once by oral gavage daily on gestational days 6-15

Method: Body weight, food consumption, clinical signs, pregnancy rates, and necropsy of dams; uterine contents (including implants and resorption) at day 19 of gestation, corpora lutea; fetal viability and weight, crown-rump length, external, visceral (1/3 fetuses), and skeletal abnormalities; extensive statistical analyses.

Results: High-dose dams exhibited clinical signs (urine stains, hunched appearance, and alopecia); sporadic signs of urine stains and hunched appearance occurred in a few mid-dose dams, but not at the low-dose. Food consumption was statistically lower in mid-dose dams on days 7-11 and in high-dose group throughout (days 7-15). During Days 6-11, significant ($p < 0.05$) reductions in body weight gain in mid-dose dams and mean body weight loss at the high dose; on days 11-15, only high-dose dams showed reduced body weight gain. Overall body weights reduced in high-dose dams. TDCPP had no effect on implantation efficiency or mean number of corpora lutea. Treatment at the high dose significantly ($p < 0.05$) increased the number of resorptions (to 14.4% compared to 6.7% in controls) and reduced fetal viability (to 85.6% compared to 93.3% for controls). Decreased skeletal development in the high-dose groups is related to growth retardation and decreased fetal size. The incidence of malformations was not related to treatment. The study indicates a NOAEL of 25 mg/kg/day and a LOAEL of 100 mg/kg/day for maternal toxicity (clinical signs and transient reduction in body weight gain) and a NOAEL of 100 mg/kg/day and a LOAEL of 400 mg/kg/day for developmental toxicity (increased resorptions and fetal mortality).

Reference: Hazleton, 1978

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

No studies with the specific designs of the two tests listed above were available.

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The combined chronic toxicity/carcinogenicity assay in dietarily exposed rats is consistent with the guideline (Freudenthal and Henrich, 2000; Bio/Dynamics, 1980).

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**

No studies of this type were located.

Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)

The protocol of a 2-year feeding bioassay in rats was consistent with this guideline (Freudenthal and Henrich, 2000; Bio/Dynamics, 1980). The published article focused on tumor results rather than non-neoplastic effects.

Type: Combined oral chronic toxicity and carcinogenicity assay

Species, strain, sex, number: Rat, Sprague-Dawley, 60/sex/group

Purity: 95%

Doses: 0, 5, 20, and 80 mg/kg body weight/day

Vehicle: None other than feed

Route: In feed; diets blended weekly to achieve target doses

Exposure duration, frequency: 2 years, ad lib

Method: Examined twice daily for mortality and clinical signs, weekly physical examination. Body weights and food consumption weekly for the first 13 weeks and biweekly thereafter. Ophthalmoscopic examinations every 6 months. Extensive hematology, clinical chemistry and urinalysis parameters at 3, 6, 12, 18, and 24 months. Ten/sex/dose randomly chosen for termination at 12 months; the remainder at 24 months. Gross necropsy including organ weights (8 organs plus gonads); histopathology of more than 30 tissues in control and high-dose rats; at low- and mid-doses, histopathology limited to liver, kidneys, testes, and adrenals. Statistical analyses.

Results: The following changes compared to controls were statistically significant ($p < 0.05$). Mortality increased in high-dose males (to 61.7% vs 43.3% for controls). Lower body weights in high-dose males and females. Treatment had no effect on feed consumption. Signs of anemia (lower hemoglobin, hematocrit, erythrocyte counts) in high-dose rats. At the mid-dose, increased absolute and relative kidney weight males and females, absolute liver weight and relative thyroid weight in males, and relative liver weight in females. At the high dose, increased relative liver weight in males and absolute and relative thyroid weights in females.

Increases in the incidences of the following nonneoplastic lesions were statistically significant ($p < 0.05$) in treated groups compared to the control groups; changes were not strictly dose-related in that incidences were depressed in high-dose groups. Kidney lesions (convoluted tubule hyperplasia) in males at ≥ 20 mg/kg/day and in females at 80 mg/kg/day. Other systemic lesions at 80 mg/kg/day involved the parathyroid (hyperplasia) in males and the liver (foci) and spleen (erythroid/myeloid hyperplasia) in females. Reproductive system lesions in males involved seminal vesicles (atrophy, decreased secretory product) at ≥ 5 mg/kg/day, testes (eosinophilic material in lumen, periarteritis nodosa) at ≥ 20 mg/kg/day, and epididymis (oligospermia and degenerated seminal product) at 80 mg/kg/day. (Tumor incidences are reported below under Carcinogenicity.) The authors reported the lowest dose of 5 mg/kg/day as a NOAEL and the

mid-dose of 20 mg/kg/day as a LOAEL. However, as evaluated in NRC (2000), the lowest dose of 5 mg/kg/day was a LOAEL for atrophy and decreased secretory product of the seminal vesicle.

Reference: Freudenthal and Henrich, 2000; also Bio/Dynamics (1980), fiche 27 of 32 and Bio/Dynamics (1981) fiche 6 of 6.

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Increased tumor incidences were observed in a combined chronic toxicity/carcinogenicity assay in rats exposed to TDCPP in the diet (Freudenthal and Henrich, 2000).

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**

No studies of this type were located.

Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)

A 2-year feeding bioassay by Freudenthal and Henrich (2000) was consistent with this guideline.

Type: Combined oral chronic toxicity and carcinogenicity assay

Species, strain, sex, number: Rat, Sprague-Dawley, 60/sex/group

Purity: 95%

Doses: 0, 5, 20, and 80 mg/kg body weight/day

Vehicle: None other than feed

Route: In feed; diets blended weekly to achieve target doses

Exposure duration, frequency: 2, ad lib

Method: See description above under Chronic Toxicity

Results: The following neoplastic changes compared to controls were statistically significant ($p < 0.05$). Dose-related increased incidences at ≥ 20 mg/kg/day of renal cortical adenomas in both sexes and testicular interstitial tumors in males, and at 80 mg/kg/day, of hepatocellular adenomas and carcinomas combined in both sexes and adrenal cortical adenomas in females. The NRC (2000) concluded that this study provides sufficient evidence of carcinogenicity of TDCPP in rats following chronic oral exposure.

Reference: Freudenthal and Henrich, 2000; also Bio/Dynamics (1980, 1981)

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The delayed neurotoxicity component is satisfied by the existing data, but a developmental toxicity study by Tanaka et al. (1981) that included postnatal behavioral examinations did not fully satisfy the developmental neurotoxicity component. TDCPP gave negative results in single acute and subchronic oral delayed neurotoxicity studies in hens and in limited postnatal testing in rats exposed during gestation. A 2-year feeding bioassay in rats by Freudenthal and Henrich, 2000; Bio/Dynamics, 1980), discussed above under the Chronic Toxicity and Carcinogenicity endpoints, reported no lesions of the cervical spinal cord, but a slight (not statistically significant) increase in the incidence of gliomas of the brain in rats exposed to TDCPP at 80 mg/kg/day. The study authors could not determine whether this effect was related to exposure.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute studies and one subchronic study for delayed neurotoxicity in the hen, summarized below, give no evidence of acute cholinergic toxicity, inhibition of neurotoxic esterase (NTE) activity, or delayed neurotoxicity for TDCPP. These studies, performed prior to the existence of the guidelines, do not entirely conform to current guidelines, and may lack detail such as the purity of the TDCPP sample. The lack of significant NTE inhibition following dosing with 10,000 mg/kg suggests that no additional testing for delayed neurotoxicity is needed for TDCPP.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Unpublished industrial acute (1- or 5-day) and subchronic (90-day) delayed neurotoxicity assays, which pre-date the guideline, are missing some details. One acute study employed a gavage dose 5 times higher than now specified under the guideline. The subchronic assay had a longer duration and a larger group size than specified under the guideline.

Critical Studies

Type: Acute oral delayed neurotoxicity

Species, strain, sex, number: Hen, White Leghorn, 4/dose

Purity: Fyrol FR-2, purity not reported, clear colorless liquid

Doses: 420 mg/kg (highest dose specified in protocol)

Vehicle: test substance diluted 50% in corn oil

Positive control: 90 or 120 mg/kg/day tri-ortho-tylol phosphate (TOCP)

Route: Gavage

Exposure duration, frequency: Once daily on five consecutive days

Method: Navy MIL-H-19457B (SHIPS) protocol. Hens were weighed and graded on days 7, 9, 11, 14, 16, 18, 21, and 23 after the first dose for no signs, doubtful/minor signs, positive paralytic signs, advanced paralytic signs, or death. Scores on the 21st day were compared with results for TOCP. Necropsy not performed.

Results: No overt signs of neurotoxicity in with TDCPP treatment. Positive control caused inability to walk, hypertension, ataxia, and prostration.

Reference: Bullock and Kamienski, 1972 as described in WHO, 1998; Stauffer 1972a

Type: Acute oral delayed neurotoxicity

Species, strain, sex, number: Hen, White Leghorn, 4/dose for TDCPP, 3/dose for controls

Purity: Fyrol FR-2, clear colorless liquid; one part of the report stated that the purity was not reported, whereas another part of the report indicated purity >99%.

Doses: 10,000 mg/kg

Vehicle: None

Positive control: 500 mg/kg tri-ortho-cresyl phosphate (TOCP)

Negative control: 15 mg/kg tetraethyl pyrophosphate (TEPP)

Route: Oral gavage

Exposure duration, frequency: Once

Method: Twenty minutes before dosing, hens received atropine and 2-PAM to protect against cholinergic effects. Hens were observed for toxic signs at 2-hour intervals for the first 8 hours. Mortalities were recorded after 24 hours. Brains were harvested 24 hours after dosing and analyzed for neurotoxic esterase (NTE) activity.

Results: Toxic signs were not reported specifically for TDCPP, but for all compounds tested at the maximum tolerated dose, signs included listlessness and ataxia. Inhibition of NTE activity was 7% for TDCPP and the negative control TEPP, but 85% for the positive control (TOCP). The current guideline specifies that testing is not necessary at doses above 2,000 mg/kg.

Reference: Stauffer, 1978

Type: Subchronic oral delayed neurotoxicity

Species, strain, sex, number: Hen, adult, White Leghorn, 10/dose

Purity: Not reported

Doses: 0, 4, 20, and 100 mg/kg/day

Vehicle: Not reported

Route: Oral Gavage

Exposure duration, frequency: 90 days, daily

Method: Body weight. Daily observations for mortality and behavioral changes; evaluated for signs of motor weakness 3 times per week. At termination, hens were necropsied and brain (multiple sections), sciatic nerve, and spinal cord (cervical, thoracic and lumbar) were examined histopathologically. TOCP was the positive control.

Results: Hens treated with TDCPP at the high dose exhibited mean reductions in body weight during the latter part of the study, but no overt signs of neurotoxicity and no histopathological effects in the nervous tissues. Conversely, the positive control hens exhibited consistently lower body weight gain, clinical signs of toxicity (locomotor impairment and ataxia) that became more severe with time. Histopathology results were not reported for the positive control.

Reference: Robust summary from Akzo-Nobel, 2001a; unpublished, unidentified study dated 1979

Neurotoxicity (Adult)

Conclusion:

The available adult neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The chronic oral bioassay by Freudenthal and Henrich (2000; Bio/Dynamics, 1980, 1981) reported no lesions of the brain or spinal cord in rats exposed to TDCPP at doses as high as 80 mg/kg/day for 2 years, but no functional tests of neurotoxicity were performed.

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

No studies of this type were located.

Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)

Conclusion:

The available developmental neurotoxicity data were judged inadequate to meet the endpoint, although the available tests suggest that TDCPP is not a developmental neurotoxin.

Basis for Conclusion:

No studies of this specific design were located. A Japanese-language gavage study by Tanaka et al. (1981), described above under Developmental Toxicity, included postnatal neurobehavioral tests (open field, water maze, rota rod, inclined screen, pain reflex, and Preyer's reflex) of sensory and motor function in rats. Full descriptions of these tests were not available in the

English summary and therefore could not be compared to the guideline protocol. The study reported no adverse effect in these tests for offspring of dams that were exposed on gestational days 7-15 at doses as high as 200 mg/kg/day (the highest tested non-lethal dose that was a LOAEL for increased kidney weight). This study does not fully satisfy the developmental neurotoxicity endpoint because it omitted some parameters specified under the guideline: developmental landmarks for sexual maturity, auditory startle test, and neurohistopathological examinations.

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat)
 - OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent)
 - OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred)
 - OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Conclusion: These endpoints do not appear to be applicable to TDCPP.

Basis for Conclusion: Although there are no studies addressing these endpoints, there are no reliable data for TDCPP, and no structure-activity considerations, that indicate a need for these follow-up studies.

Other Neurotoxicity Data

Cholinesterase inhibition

Fyrol FR-2 administered at 0, 2,000, or 3,980 mg/kg in corn oil was administered to groups of 10 male Sprague-Dawley rats by oral gavage had no effect on plasma or erythrocyte cholinesterase levels measured 4 or 14 hours after dosing (Stauffer, 1972b).

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only study evaluating the potential immunotoxicity of TDCPP (Luster et al., 1981) predates the guideline for immunotoxicity (note that the OPPTS guideline cites other works by this author). There is some uncertainty as the test material, reported as Fyrol FR2, but mis-identified by the authors as tris(2,3-dichloropropyl) phosphate. The study methods differed from the guideline in the short exposure period (4 rather than 28 days), parenteral administration (rather than oral or inhalation route), measurement of serum immunoglobulins in non-immunized rather than immunized mice, and the omission of some tests (enumeration of immunological cell subpopulations, test for NK-cell activity). The results do not provide dose–response information as to immunotoxicity of TDCPP following subchronic exposure by oral or inhalation routes of exposure.

Immunotoxicity (OPPTS Harmonized Guideline 870.7800)

Critical study

Type: Immunotoxicity, subcutaneous, acute

Species, strain, sex, number: Mouse, B6C3F₁, 6-8 females/dose

Doses: 0, 0.25, 2.5, or 25 mg/kg/day (Total cumulative doses of 0, 1, 10, or 100 mg/kg)

Identity: Stauffer Fyrol FR-2, lot 4670-3-23. This is the same lot as TDCPP tested in the 2-year oral assay by Freudenthal and Henrich (2000)

Purity: Stauffer, purity >95%

Vehicle: Corn oil

Route: Subcutaneous injection

Exposure duration, frequency: 4 days, once daily

Method: Observations included body weight, hematology, clinical chemistry (5 parameters) terminal necropsy, organ weights (liver, spleen and thymus), histopathology of spleen, thymus, and eight other organs, plaque-forming assay response to sheep red blood cells, and serum immunoglobulin quantification (non-immunized mice only). Non-guideline tests included proliferative capacity of granulocyte-macrophage progenitor cells (bone marrow), *in vitro* lymphoproliferative (LP) responses to mitogens, delayed hypersensitivity response to keyhole limpet hemocyanin. Extensive statistical analysis.

Results: Twenty percent of high-dose mice exhibited lymphoid depletion of the thymus. Statistically significant decreases *in vitro* lipopolysaccharide (B-cell antigen) at 2.5 mg/kg/day and concanavalin A (T-cell antigen) at 25 mg/kg/day.

Reference: Luster et al., 1981

GENOTOXICITY

Conclusion: The available genotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

TDCPP has been tested in *in vitro* and *in vivo* genotoxicity assays conducted in prokaryotic and eukaryotic cells under methods similar to guidelines. Results of *in vivo* tests (mutation in *Drosophila*, chromosomal aberration in mice) were negative, but positive results were reported in several *in vitro* assays (mutagenicity in bacterial and mammalian cells, chromosomal aberration).

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

Type: Bacterial reverse mutation

Species, strain: *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537

Metabolic activation: Tested with and without S9 from livers of Aroclor-induced male Sprague-Dawley rats or male Hamsters

Concentrations: 0, five concentrations between 10 and 10,000 µg/plate.

Purity: 94.4%

Method: Preincubation (20 minutes) and plate incorporation (48 hours) at 37°C. Positive controls were used; DMSO was the solvent. Triplicate plates per concentration. All assays repeated within 1 week.

Results: In three different laboratories, TDCPP tested positive in strains TA97 and TA100 in the presence of S9 from Aroclor-induced hamster liver and in strain TA1535 in the presence of S9 from Aroclor-induced rat or hamster liver. Positive controls gave expected increases. Solvent control and all other test combinations were negative.

Reference: Mortelmans et al., 1986

Type: Bacterial reverse mutation

Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538

Metabolic activation: Tested with and without Kanechlor 500 (PCB)-induced liver S9 from male Wistar rats

Concentrations: 0, 10, 30, 100, and 300 µg/plate.

Purity: Assayed as ~94% TDCPP, plus ~6% bis(1-chloromethyl-2-chloroethyl)(2,3-dichloropropyl) phosphate.

Method: Plate incorporation, 48-hour incubation at 37°C. Cited Ames protocol, which presumes the use of replicates and positive controls.

Results: No increase in revertants in any strain without activation or in strains TA98, TA1537, or TA1538 with activation. Weak increases in TA100 and TA1535 at the highest concentrations with S9.

Reference: Nakamura et al., 1979

Additional Studies

Other *S. typhimurium* assays in which S9 was prepared from phenobarbital-induced rat liver reported mutagenicity of TDCPP in strain TA98 by liquid preincubation assay (Abe and Urano, 1994) and in TA100 by plate incorporation assay (Gold et al., 1978; Soederlund et al., 1985). Majeska and Matheson (1983) reported dose-related positive results for TDCPP and its metabolite 1,3-dichloro-2-propanol in TA100 with S9 (phenobarbital-induced) in standard plate assays at concentrations up to 500 µg/plate. In a liquid preincubation quantitative assay, results for TDCPP were essentially negative—only increasing mutation frequencies at cytotoxic concentrations (survival <3%). However, its metabolites increased mutant frequencies with less cytotoxicity: 1,3-dichloro-2-propanone positive at <80% survival and 1,3-dichloro-2-propanol positive at <30% survival.

TDCPP was not mutagenic in *S. typhimurium* strains TA100, TA1535, or TA1538 without activation or when Aroclor-induction was used to prepare the S9 fraction (Prival et al., 1977); the highest exposure level was 10 µL per plate.

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

Type: Mammalian Cell Gene Mutation Test: Forward Mutation

Species, strain: Mouse lymphoma L5178Y

Metabolic activation: Tested with and without phenobarbital-induced liver S9 from male mice

Concentrations: 0, and five concentrations up to ~32 nL/mL without S9, and six concentrations up to 70 nL/mL with S9. Test conditions chosen based on preliminary assays so that 50% growth reduction occurred at highest concentration.

Purity: Not reported

Method: Selection of forward mutation from TK+/- to TK-/- genotype. Activity compared to tris(2,3-dibromopropyl)phosphate (TBPP).

Results: TDCPP yielded negative results with or without activation. TBPP was negative without, but positive with activation.

Reference: Brusick et al., 1979; also Litton Bionetics, Inc., 1977

Type: Mammalian Cell Gene Mutation Test: Forward Mutation

Species, strain: V79 Chinese hamster lung cells

Metabolic activation: Tested with phenobarbital-induced liver S9 from male rats

Concentrations: 0, 0.02 mM TDCPP. Test conditions chosen based on preliminary assays.

Purity: Not reported

Method: In two experiments, selection of 6-thioguanine-resistant colonies. Activity compared to tris(2,3-dibromopropyl)phosphate (TBPP).

Results: TDCPP with S9 did not increase mutation frequency. TBPP yielded positive results.

Reference: Soederlund et al., 1985

Gene Mutation in Vivo:

- **Sex-linked Recessive Lethal test in *Drosophila melanogaster* (OPPTS Harmonized Guideline 870.5275)**

Type: Sex-linked Recessive Lethal test

Species, strain: *Drosophila melanogaster*, 100 males/concentration

Metabolic activation: None

Concentrations: 2.5 and 25% in feed (1% gum tragacanth in 3% sucrose)

Purity: Technical-grade Fyrol FR-2, purity not reported

Method: TDCPP added to feed of males for 24 hours, subsequently mated with virgin unexposed females

Results: No evidence of toxicity or increase in the percentage of sex-linked recessive lethal mutations.

Reference: Brusick and Jagannath, 1977 as described in WHO, 1998; also Litton Bionetics, Inc., 1976

Chromosomal Aberration in Vitro:

- **In Vitro Mammalian Chromosome Aberration Test (OPPTS Harmonized Guideline 870.5375)**

Type: *In vitro* chromosome aberration assay

Species, strain: Mouse lymphoma L5178Y

Metabolic activation: None, phenobarbital-induced or PCB-induced

Concentrations: 0, 0.01 to 0.1 µL/mL for non-induced, phenobarbital-induced or PCB-induced mouse

Purity: Not reported

Method: 4-hour exposure to TDCPP with or without activation. Chromosomal aberrations scored in 50 metaphase spreads per concentration.

Results: TDCPP caused increases chromosomal aberrations (up to 40%) with PCB- or phenobarbital-induction compared to noninduced S9.

Reference: Brusick et al., 1979; also Litton Bionetics, Inc., 1977

Additional Information

One confidential study reported negative results for TDCPP in cultured Chinese hamster ovary cells with or without metabolic activation. Another confidential study reported positive results in human lymphocytes with metabolic activation.

- **In vitro Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5900)**

Type: *In vitro* sister chromatid exchange assay

Species, strain: Mouse lymphoma L5178Y

Metabolic activation: None, phenobarbital-induced or PCB-induced

Concentrations: 0, 0.005-0.03 µL/mL for phenobarbital-induced (4 concentrations), and 6 concentrations up to 0.070 µL/mL for non-induced or PCB-induced mouse

Purity: Not reported

Method: Ten cells per concentration were analyzed.

Results: TDCPP increased the incidence of sister chromatid exchanges in mouse lymphocytes under all three test conditions.

Reference: Brusick et al., 1979; also Litton Bionetics, Inc., 1977

Additional Information

One submitted confidential study reported negative results in a sister chromatid exchange assay. The data for this study are not adequate because the cell line was not identified. Fyrol FR-2 did not induce sister chromatid exchanges when applied to 3- to 4-day-old chicken embryos (Bloom, 1984).

Chromosomal Aberration in Vivo:

- **Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)**

The available study provides sufficient evidence that TDCPP did not induce chromosomal aberrations in mice exposed at the maximum tolerated dose of 760 mg/kg.

Type: Bone marrow chromosomal aberration *in vivo*

Species, strain: Mouse, CD-1, 4-8 males/group

Metabolic activation: None

Concentrations: 0, 0.05, 0.17, and 0.5 mL/kg; using the specific gravity of 1.52, the doses were 0, 76, 260, or 760 mg/kg. The highest dose was the maximum tolerated dose. Negative control was DMSO

Exposure duration, frequency: By oral gavage in once or daily on 5 consecutive days.

Purity: Technical grade; Not reported

Method: Mice were sacrificed at 6, 24, and 48 hours after single dose or 6 hours after the last of 5 doses. Between 233 and 400 cells were scored, rather than 500/animal. Triethylenemelamine was positive control.

Results: No evidence of increased frequency of chromosomal aberrations with TDCPP. TBPP was also negative at doses up to 1,000 mg/kg. Positive control produce expected large increase in micronucleated polychromatic erythrocytes.

Reference: Brusick et al., 1979; Litton Bionetics, Inc., 1978

- **Mammalian erythrocyte micronucleus test (OPPTS Harmonized Guideline 870.5395)**

TDCPP administered as 2,000 mg/kg by an unspecified route to mice did not induce micronuclei in bone marrow erythrocytes (Thomas and Collier, 1985 as reported in WHO, 1998).

DNA Damage and Repair

- **Unscheduled DNA synthesis in mammalian cells in culture (OPPTS Harmonized Guideline 870.5550)**

Type: Unscheduled DNA synthesis in mammalian cells (hepatocytes) in culture

Species, strain: Rat, Wistar, male

Metabolic activation: With or without phenobarbital-induction

Concentrations: 0, 0.05, and 0.1 mM

Purity: Not reported

Vehicle: DMSO

Method: Cultured hepatocytes exposed to TDCPP or TBPP for 18-19 hours. Incorporation of radiothymidine into DNA.

Results: TDCPP was not genotoxic at 0.05 mM, but at 0.1 mM, a moderate response was observed in hepatocytes from untreated rats, but not phenobarbital-treated rats. TBPP, the positive control, yielded positive results in induced and non-induced hepatocytes.

Reference: Soederlund et al., 1985

Additional Information

A confidential study reported negative results for TDCPP and its metabolites (not identified) in cultured primary hepatocytes from male Sprague-Dawley rats.

Ecotoxicity

Aquatic Organism Toxicity

Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)

Conclusion:

The available acute toxicity data for freshwater fish (cold- and warm-water species) and saltwater fish were judged inadequate to meet the endpoint. The available acute fish toxicity studies are summarized in Table 3-1. However, if the results of the SafePharm study (1993a), cited by IPCS (1998) (see below), are confirmed independently, the acute toxicity data for cold freshwater fish species might meet the endpoint given the high degree of agreement of the two available studies in rainbow trout.

Basis for Conclusion:

Freshwater Fish

Ahrens et al. (1979) tested the toxicity to goldfish (*Carassius auratus*) of tris (1,3-dichloro-2-propyl) phosphate (TDCPP) released from fabric treated with the flame retardant. Laundered or unlaundered sections of garment that had been treated with Fyrol FR-2, were placed in tanks with six goldfish. Fish in the tank with the unlaundered section became sluggish and all died within 3 hours. The concentration of Fyrol FR-2 in the test water reached 30 mg/L. Fish exposed for 96 hours to the laundered section of garment did not exhibit signs of toxicity. In another study, TDCPP in water at 1 mg/L was not toxic to goldfish after 168 hours, but 5 mg/L of TDCPP killed all (6/6) goldfish within 24 hours (Eldefrawi et al., 1977). The studies by Ahrens et al. (1979) and Eldefrawi et al. (1977) did not evaluate toxicity using a range of concentrations of TDCPP in water and, thus, cannot be used to derive an LC₅₀.

Sasaki et al. (1981) estimated that the 96-hour LC₅₀ values for killifish (*Oryzias latipes*) and goldfish were 3.6 mg/L and 5.1 mg/L, respectively. It appears that mortality was not evaluated in a control group of fish. It is unclear if the TDCPP concentrations in water reported by Sasaki et al. (1981) are measured or nominal values. The latter point is important because a parallel study indicated that the amount of TDCPP added to test water declines rapidly and less than 40% of the original amount of TDCPP remains in the test water after 96 hours (Sasaki et al., 1981). Thus, the lethal concentrations of TDCPP could be lower than the reported LC₅₀ values. Sasaki et al. (1981) reported deformation of the spine in 7/10 killifish exposed to 3.5 mg/L TDCPP for 24 hours. However, Sasaki et al. (1981) do not provide sufficient information regarding the spine deformation in killifish to make meaningful use of these observations. It is unclear whether the deformations were observed in the acute toxicity study or in a separate assay using killifish only. It appears that deformation was tested at only one concentration and a control group of fish was not evaluated.

Another study showed that the 96-hour LC_{50} of TDCPP in rainbow trout (currently classified as *Oncorhynchus mykiss*) was 1.4 mg/L (95% CI: 0.9-1.9 mg/L) (Unpublished study conducted in 1990, summarized in Akzo-Nobel, Inc., 2001a,b). A NOEC was not observed since one fish died at 0.63 mg/L, the lowest concentration tested. Compound purity was not provided in the summary and the reported concentrations of TDCPP in the test water appear to be nominal values. The guideline for acute toxicity in fish (OPPTS 850.1075) indicates that test concentrations must be measured during the test if, as was the case in this study, aeration is used. Thus, the study reported by Akzo-Nobel, Inc. (2001a,b) does not meet the criteria established by the guideline. The studies by Sasaki et al. (1981) and Akzo-Nobel, Inc. (2001a,b) suggest that the 96-hour LC_{50} for TDCPP in fish is in the range of 1 to 5 mg/L, making it moderately toxic to fish. However, the data are inadequate to satisfy the acute toxicity endpoint for freshwater fish. A 96-hour LC_{50} of 1.1 mg/L and a NOEC of 0.56 mg/L for TDCPP in rainbow trout (SafePharm, 1993a) were reported in IPCS (1998). Although the results of the study by SafePharm (1993a) are in agreement with those of Akzo-Nobel, Inc. (2001a,b), the study by SafePharm (1993a), or a study summary, was not available to allow for an independent evaluation of these data. Confirmation of the results of the study by SafePharm (1993a) might allow the acute toxicity endpoint for freshwater fish to be satisfied.

Marine Fish

No acute toxicity studies in saltwater fish species were located.

Table 3-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)^a

Study Reference	Species Tested	96-Hour LC ₅₀	Selected Study Design Parameters ^b						Comments on the Data
			Study Type	Concentrations Tested	No. of Fish/ Conc	Analytical Monitoring	Water Chemistry	Solvent	
Ahrens et al., 1979	Goldfish (<i>Carassius auratus</i>)	None	Static	None	6	Yes. The concentration of Fyrol FR-2 in water was determined by gas chromatography.	pH: NR Temp: 20°C DO: NR Hardness: NR Water volume: 20 L Electrical conductivity: 290 micromhos/cm	None	<p>A laundered or unlaundered 38 cm x 64 cm section of garment (0.24 square meter area; 227 g/m³), which had been treated with Fyrol FR-2, was placed in tanks with six goldfish.</p> <p>Fish in the tank became progressively more sluggish and all died within 3 hours. The measured concentration of Fyrol FR-2 in the test water was 30 mg/L.</p> <p>Fish exposed for 96 hours to the same section of fabric after it had been laundered did not die.</p> <p>Data for mortality in control fish were not presented in the study.</p> <p>Goldfish are not a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine).</p> <p>The study cannot be used</p>

Table 3-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8) ^a									
Study Reference	Species Tested	96-Hour LC ₅₀	Selected Study Design Parameters ^b						Comments on the Data
			Study Type	Concentrations Tested	No. of Fish/ Conc	Analytical Monitoring	Water Chemistry	Solvent	
Akzo-Nobel, Inc., 2001a,b (Study conducted in 1990)	Rainbow trout (<i>Salmo gairdneri</i>)	1.4 mg/L (95% CI: 0.9-1.9 mg/L)	Static	Controls, 0.63, 1.25, 2.5, 5, 10 mg/L	10	No	pH: 7.14-7.78 Temp: 11.8-14.8 °C. DO: 92-100% of air saturation value Hardness: 218-228 mg/L as CaCO ₃ .	None reported	All mortalities occurred within the first 24 hours. Mortality was dose related. One fish died in the lowest dose group (0.63 mg/L). All fish died in the 5 and 10 mg/L groups. A NOEC was not observed.

Table 3-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8) ^a									
Study Reference	Species Tested	96-Hour LC ₅₀	Selected Study Design Parameters ^b						Comments on the Data
			Study Type	Concentrations Tested	No. of Fish/ Conc	Analytical Monitoring	Water Chemistry	Solvent	
Eldefrawi et al., 1977	Goldfish (<i>Carassius auratus</i>)	None	Static	1 and 5 mg/L in water	6	None reported	<p>pH: NR</p> <p>Temp: 20°C</p> <p>DO: NR</p> <p>Hardness: NR</p> <p>Electrical conductivity: 290 micromhos/cm</p>	Water or acetone	<p>Fish were exposed to 1 or 5 mg/L TDCPP in water or acetone. None of the fish in the 1 mg/L treatment had died after 168 hours.</p> <p>All fish in the 5 mg/L treatment died within 24 hours.</p> <p>The most conspicuous signs of toxicity were sluggishness and disoriented swimming prior to death.</p> <p>Mortality in control fish was not reported.</p> <p>Goldfish are not a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine).</p> <p>The study cannot be used to establish an LC₅₀ value.</p>

Table 3-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8) ^a									
Study Reference	Species Tested	96-Hour LC ₅₀	Selected Study Design Parameters ^b						Comments on the Data
			Study Type	Concentrations Tested	No. of Fish/ Conc	Analytical Monitoring	Water Chemistry	Solvent	
Sasaki et al., 1981	Killifish (<i>Oryzias latipes</i>)	Killifish: 3.6 mg/L	Static	NR	7 to 9	Unclear if conducted	pH: NR Temp: 25°C. DO: NR Hardness: NR Electrical conductivity: NR	NR	Fish were acclimated at least for 10 days at 25 °C. The test concentrations used were not reported. A control group was not tested. Killifish, but not goldfish, are a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine). Deformation of the spine was observed in 7/10 killifish exposed to 3.5 mg/L TDCPP for 24 hours.
	Goldfish (<i>Carassius auratus</i>)	Goldfish: 5.1 mg/L							

^aStudies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.
^bNR: Not reported

Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD 202)

Conclusion:

The available acute toxicity data for freshwater invertebrates were judged inadequate to meet the endpoint. However, if the results of the study cited by IPCS (1998) (see below) are confirmed independently, the data might meet the endpoint given the high degree of agreement of the two available studies in freshwater invertebrates.

Basis for Conclusion:

The available data are summarized in Table 3-2. A flow-through study revealed a 48-hour LC₅₀ of TDCPP with *Daphnia magna* of 3.8 mg/L (95% CI: 3.5-4.2 mg/L) and a NOEC of 1.6 mg/L (Unpublished study conducted in 1999, summarized in Akzo-Nobel, Inc., 2001a,b). Although some of the conditions of the study design (such as number of organisms, and water temperature and chemistry) appear to meet OPPTS Harmonized Guideline 850.1010, other aspects of the study, including compound purity and condition and fertility of the organisms in culture, were not reported in the summary. The amount of solvent used in the control group and the TDCPP treatments might have exceeded the recommended maximum solvent concentration, as per the OPPTS Guideline (100 mg/L), but this does not appear to have affected the study results. A 48-hour LC₅₀ of 4.6 mg/L and a NOEC of 1.8 mg/L were reported for daphnia in a study by SafePharm (1993b), as cited in IPCS (1998). Although the results of the study by SafePharm (1993b) are in agreement with those of Akzo-Nobel, Inc. (2001a,b), the study by SafePharm (1993b), or a study summary, was not available to allow for an independent evaluation of these data. Confirmation of the results of the study by SafePharm (1993b) might allow the acute freshwater invertebrate toxicity endpoint to be satisfied.

Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)

Conclusion:

No available acute marine/estuarine invertebrate toxicity data.

Basis for Conclusion:

No acute toxicity studies in marine/estuarine invertebrate species were located.

Table 3-2. Summary of available acute invertebrate toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)^a

Study Reference	Species Tested	48-Hour LC ₅₀	Selected Study Design Parameters						Comments on the Data
			Study Type	Concentrations Tested	No. of Organisms/ Concentration	Analytical Monitoring	Water Chemistry	Solvent	
Akzo-Nobel, Inc., 2001a,b (Study conducted in 1999)	<i>Daphnia magna</i>	3.8 mg/L (95% CI: 3.5-4.2 mg/L)	Flow-through	Negative control, solvent control (dimethylformamide), 0.98, 1.6, 2.8, 3.8, 5.1 mg/L	10	Yes	pH: 8.3 Temp: 20±2°C DO: ≥8.5 mg/L (94% of air saturation value) Hardness: 126 mg/L as CaCO ₃ .	Dimethylformamide	<p>Daphnids in the negative and solvent control groups appeared normal, as did the organisms in the 0.98 and 1.6 mg/L groups. Mortality in the 2.8, 3.8, and 5.1 mg/L groups was 0, 70, and 80%, respectively. Daphnids (15%) in the 2.8 mg/L group were lethargic at study termination.</p> <p>The amount of solvent used in the control group and the TDCPP treatments is estimated to be approximately 300 mg/L. This exceeds the recommended maximum solvent concentration of 100 mg/L. The estimate is based on a reported dimethylformamide volume of 0.1 ml, a test chamber volume of 300 ml and a specific gravity of 0.95.</p>

^aStudies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.

Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)

Conclusion:

No available chronic toxicity data for freshwater and marine fish.

Basis for Conclusion:

No chronic toxicity studies in freshwater and marine fish were located.

Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD 211) and Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)

Conclusion:

No available chronic toxicity data for freshwater and marine/estuarine invertebrates.

Basis for Conclusion:

No chronic toxicity studies in freshwater and marine/estuarine invertebrates were located.

Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)

Conclusion:

The available algal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are summarized in Table 3-3. The summary of a 96-hour algal toxicity study (Unpublished study conducted in 1992, summarized in Akzo-Nobel, Inc., 2001a,b) indicates that the study does not meet the OPPTS Harmonized Guideline 850.5400. The pH and temperature of the test water during the study were outside of the acceptable ranges for *Selenastrum capricornutum*, as per Guideline 850.5400. Moreover, the two highest concentrations tested exceed the estimated water solubility of TDCPP (42 mg/L) and the concentrations tested were apparently not verified analytically. Additional information, including test substance purity, hardness, DO, TOC, TSS, exposure vessel size and head space, and measured chemical concentrations, were not provided in the summary. Also, there is no evidence that positive controls were used in order to establish that the algae were responding in the expected manner to a known chemical. The deviations from the OPPTS Guideline indicate that the study is inadequate to satisfy the algal toxicity endpoint. Another study indicates that TDCPP at 10 mg/L had no effect on growth or biomass of the algal species *Scenedesmus subspicatus* exposed for 72

hours (Unpublished study conducted by SafePharm, 1994, cited in IPCS, 1998). The study, or a study summary, was not available for the study by SafePharm (1994) to allow for an independent evaluation of these data.

Table 3-3. Summary of available algal toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8) ^a								
Study Reference	Species Tested	EC ₅₀ , NOAEC, and LOAEC	Selected Study Design Parameters ^b					Comments on the Data
			Study Type	Concentration Range Tested	Analytical Monitoring	Water Chemistry	Solvent	
Akzo-Nobel, Inc., 2001a,b (Study conducted in 1992)	<i>Selenastrum capricornutum</i>	96-hour EbC ₅₀ (biomass) = 12 mg/L (95% CI: 10-15 mg/L). 96-hour ErC ₅₀ (growth rate) = 39 mg/L (95% CI: 31-50 mg/L). 96-hour NOAEC: 6 mg/L.	Static	0 (negative control), 2, 6, 18, 54, or 162 mg/L	No	Temp: 21°C pH: 6.7-7.9 DO: NR Hardness: NR	None reported	A number of problems are evident with this study, namely the pH changed markedly during the study, and the reported pH and water temperature were outside of the recommended values for this algal species.
^a Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.								
^b NR: Not reported.								

Terrestrial Organism Toxicity

Acute Oral (OPPTS Harmonized Guideline 850.2100), Dietary (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205), or Reproductive Toxicity (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206) in Birds

Conclusion:

No available acute oral, dietary, and reproductive toxicity data.

Basis for Conclusion:

No acute oral, dietary, or reproductive toxicity studies in birds were located.

Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)

Conclusion:

The available earthworm subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No earthworm subchronic toxicity studies were located. An acute (14-hour) LC₅₀ of 130 mg/kg soil and a NOEC of 100 mg/kg soil with the earthworm, *Eisenia fetida* (SafePharm, 1996), were reported in IPCS 1998. However, the study has also been reported to be a 14-day subchronic toxicity study (NICNAS, 2001). The study, or a study summary, was not available for an independent evaluation of the study and the results.

Physical/Chemical Properties

Tris(1,3-dichloro-2-propyl) phosphate

CAS 13674-87-8

MF $C_9H_{15}Cl_6O_4P$

MW 430.91

SMILES ClCC(CCl)OP(=O)(OC(CCl)CCl)OC(CCl)CCl

Physical/Chemical Properties

Water Solubility:

Conclusion: The available water solubility data are adequate.

Basis for Conclusion: The key study (highlighted) was performed according to a reliable method, and is in reasonable agreement with other values reported in the literature.

Solubility (mg/L)	References
42	Akzo Nobel, 2001a,b: Water Solubility determination according to OECD Guideline 105 (shake-flask method)
7	Aston et al., 1996 (24°C); Hollifield, 1979; SRC, 2004 (PHYSPROP Database, 24°C); HSDB, 2003 (24°C)
100	Eldefrawi et al., 1977; WHO, 1998 (30°C); Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)
110	CERI, 1999
18.1	Confidential submitted study using shake flask method

Log K_{ow}:

Conclusion: The available log K_{ow} data are adequate.

Basis for Conclusion: The key study (highlighted) was performed according to a reliable method.

Log K _{ow}	Reference
2.4	Akzo Nobel, 2001a,b: Determination of Octanol-Water Partition Coefficient According to OECD Guideline 117 (HPLC Method)
3.8	WHO, 1998
3.65	SRC, 2004 (PHYSPROP Database); HSDB, 2003
3.75	Shake-flask method, Sasaki et al., 1981
3.69	Confidential submitted study using the HPLC method

Oxidation/Reduction: No data

Melting Point:

Conclusion: The available melting point data for TDCPP are adequate.

Basis for Conclusion: The key study (highlighted) was performed according to a reliable method. It is noted that the other literature data do not agree with the key study; however, the methods used to measure the melting points are not provided in any of the sources. As an OECD-guideline compliant method, the key study is better described and better supported.

Melting Point (°C)	References
-58	Akzo Nobel, 2001a,b: melting point determination by DSC (compliant with OECD Guideline 102), freezing point was determined to be -40°C, melting point -58°C
27	CERI, 1999
26.66	Akzo Nobel, 2003

Boiling Point:

Conclusion: The boiling point data are adequate.

Basis for Conclusion: A variety of literature sources report the same value for the boiling point, although there is some indication that the compound may decompose at or near the boiling point. Since experimental details are not provided in any of the sources, it is not possible to determine whether the temperatures reported are decomposition or boiling temperatures. Nevertheless, given the high boiling point reported for this material, the available data are adequate to characterize its potential volatility.

Boiling Point (°C/torr)	References
236-237/5	SRC, 2004 (PHYSPROP database); Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials); WHO, 1998
200/4	Akzo Nobel, 2003
Dec. >200/4	WHO, 1998
Gradual Dec. >200	HSDB, 2003

Vapor Pressure:

Conclusion: The available vapor pressure data are not adequate

Basis for Conclusion: Although this measured vapor pressure is reported in two sources, it appears to be very high relative to the boiling points reported for this chemical. For comparison, an estimated vapor pressure (EPIWIN) is also included in the table below. The vapor pressure remains a data need.

Vapor Pressure (torr/°C)	Reference
0.01/30	WHO, 1998; Akzo Nobel, 2001a,b
2.98 x10 ⁻⁷	EPIWIN, 2000; v. 3.11 estimate

Odor:

Conclusion: The odor of this compound has been adequately characterized.

Basis for Conclusion: Although no standardized tests are available for characterizing chemical odors, the two descriptions found are similar, and are consistent with the low volatility expected for this chemical.

Odor	Reference
Mild Odor	HSDB, 2003
Bland Odor	Akzo Nobel, 2003

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:

Conclusion: The flammability (as the flash point and autoignition temperature) has been adequately characterized.

Basis for Conclusion: Studies on the flash point and autoignition temperature of this chemical were located and appear reasonable given the other physical/chemical properties available for this compound.

Flash Point	Reference
252°C (coc)	WHO, 1998; HSDB, 2003
>107.22°C (Seta closed cup)	Akzo Nobel, 2003

Autoignition Temperature	Reference
512.77°C	Akzo Nobel, 2003

Explosivity: No data

Corrosion Characteristics: No data

pH:

This chemical does not contain functional groups expected to influence the pH of aqueous solutions. Data for this endpoint are therefore not applicable.

UV/Visible Adsorption: No data

Viscosity:

Conclusion: The viscosity of this chemical at various temperatures has been adequately characterized.

Basis for Conclusion: Studies on the viscosity of this chemical were located and appear reasonable given the other physical/chemical properties available for this compound.

Viscosity (cP)	Reference
1,800 at 25°C	WHO, 1998; Akzo Nobel, 2003
2,200 at 0°C	Akzo Nobel, 2003
540 at 40°C	Akzo Nobel, 2003

Density/Relative Density/Bulk Density:

Conclusion: The density of this compound has been adequately characterized.

Basis for Conclusion: Consistent data are provided in several reputable sources.

Density	Reference
1.52 at 25°C	Specific gravity. WHO, 1998
1.5022 at 20°C	Specific gravity. Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)
1.48 kg/L at 25°C	Bulk density. HSDB, 2003

Dissociation Constant in Water:

This compound does not have functional groups that are expected to dissociate in water. This endpoint is therefore not applicable.

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish:

Conclusion: The bioconcentration factor has been adequately characterized.

Basis for Conclusion: The two studies cited in the table below provide consistent information for killifish under both static and flow-through conditions, over a variety of observation times, and with varying initial concentrations of test substance. The BCF was also measured in goldfish; the reported BCFs are independent of study length.

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. type	Range (ppb)	Study length	T (°C)	
Sasaki et al., 1981	Killifish	113 110 77	Static	1,000 initial	24 hours 55 hours 96 hours	25	Half-life for elimination of the test compound in water + fish = 31 hours.
Sasaki et al., 1981	Goldfish	5 3	Static	1,000 initial	24 hours 96 hours	25	Half-life for elimination of the test compound in water + fish = 42 hours.
Sasaki et al., 1982	Killifish	46±5 32±4 31±6 59±16 49±12	Flow-through (all)	400 300 40 40 80	3 days 4 days 6 days 30 days 32 days	25	BCF is independent of concentration; continuous (flow-through) results correlate to static results (Sasaki et al., 1981).

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism:

Conclusion: The metabolism of TDCPP in fish is not adequately characterized in the literature.

Basis for Conclusion: The depuration rate is adequately described in killifish, however, the metabolite distribution is not addressed.

Species	Rate	Comment	Reference
Killifish	Elimination half-life, 1.65 hours	Depuration rate - elimination of TDCPP when exposed fish are moved to clean water.	Sasaki et al., 1982
Killifish	Apparent metabolism is much faster in killifish than in goldfish. (Quantitative data are not provided.)	~10% of applied TDCPP remains in the water in the presence of killifish after 96 hours. Control (no fish) has no change in TPP concentration.	Sasaki et al., 1981
Goldfish	Apparent metabolism is much slower than in killifish. (Quantitative data are not provided.)	~25% of applied TDCPP remains in the water after 96 hours in presence of goldfish.	Sasaki et al., 1981

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation:

Conclusion: The biodegradation of TDCPP under aerobic conditions has been adequately characterized.

Basis for Conclusion: The key study (highlighted) was performed according to a GLP-compliant OECD guideline test. The other data located in the literature are generally in agreement with the key study.

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
OECD Guideline 301B Modified Sturm Test	Activated sludge		0% by CO ₂ evolution. DOC red. not calculated due to solubility issues.	28 days	Initial concentrations 2, 10 mg/L. GLP- compliant. Also reported: 1) Closed bottle test (OECD Guideline 301D) showed no inhibition of bacterial cultures in 10 days.	Akzo Nobel, 2001a,b; Akzo Chemicals Incorporated, 1990

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
Japanese MITI test	Activated sludge		avg. 1% by BOD	28 days	Initial concentrations 100 mg/L (test substance), 30 mg/L (sludge).	CERI, 1999; HSDB, 2003; Chemicals Inspection and Testing Institute, 1992
OECD 302C			0% by O ₂ uptake	28 days		WHO, 1998
River Die-Away	Water from Oh River (Osaka, Japan) Neya River (Osaka, Japan) Seawater (Osaka Bay)		12.5% 18.5% 0% 5.4% 0% 22%	7 days 14 days 7 days 14 days 7 days 14 days	Initial concentrations 20 mg/L in Oh River water and 1 mg/L in Neya River water. Concentration in seawater not reported. Analysis by Molybdenum Blue calorimetric assay for increase in phosphate ion.	WHO, 1998

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis:

Conclusion: The available pyrolysis data are not adequate.

Basis for Conclusion: Although a semi-quantitative description of the pyrolysis products is given in the Choudry and Hutzinger paper, the list of degradates provided accounts for only 60% of the total mass expected and doesn't contain any oxygenated or phosphorus-containing compounds. Therefore, this study does not provide a complete profile of the pyrolysis of TDCPP.

Pyrolysis Products	Reference
Relative mol.% degradates, 0.1 mole TDCPP heated at 250-260°C under reduced pressure (3 mm Hg), overall yield 60 wt%: <i>trans</i> -1,3-dichloropropene 26.7%, <i>cis</i> -1,3-dichloropropene 36.0%, 1,2,3-trichloropropane 34.4%, 1-chloro-2-propene 2.9%.	Choudhry and Hutzinger, 1982
Thermal oxidative degradation in air at 370°C: Hydrogen halides, halogenated C2 and C3 species, acrolein	HSDB, 2003

Pyrolysis Products	Reference
When heated to decomposition, it emits toxic fumes of Cl ⁺ and PO _x	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)

Hydrolysis as a Function of pH:

Conclusion: The hydrolysis rate data are adequate. The hydrolysis products are not described.

Basis for Conclusion: The studies cited below were GLP-compliant tests run according to accepted guidelines.

T _{1/2}	pH	Temp.	Comment	Reference
>1 year >1 year 14.7 days	4 7 9	50°C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Initial concentration, 10 mg/L. Study length, 5 days. Preliminary study.	Akzo Nobel, 2001a,b
28 days	9	40°C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Definitive 30-day study.	Akzo Nobel, 2001a,b
128 days	9	20°C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Definitive 30-day study.	Akzo Nobel, 2001a,b

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

References

- Abe, A; Urano, K. 1994. Influence of chemical commonly found in a water environment on the *Salmonella* mutagenicity test. *Sci. Total Environ.* 153: 169-175.
- Ahrens, VD; Maylin, GA; Henion, JD; et al. 1979. Fabric release, fish toxicity, and water stability of the flame retardant Fyrol FR-2. *Bull. Environ. Contam. Toxicol.* 21: 409-412.
- Akzo Chemicals Incorporated. 1990. Letter from Akzo Chemicals Incorporated to USEPA submitting enclosed reports on 2-propanol-(1,3-dichloro) phosphate and ethanol-(2-chloro) phosphate with attachments. TSCA Section 8D Submission, OTS05028355.
- Akzo-Nobel, Inc. 2001a. Test plan and robust summaries for Fyrol FR-2 (CAS No. 13674-87-8). Original Submission to U.S. EPA HPV Challenge Program. (Robust summaries do not identify the sources of unpublished studies.)
- Akzo-Nobel, Inc. 2001b. Test plan and robust summaries for Fyrol FR-2 (CAS No. 13674-87-8). Revised Submission to U.S. EPA HPV Challenge Program. (Robust summaries do not identify the sources of unpublished studies.)
- Akzo Nobel. 2003. Akzo Nobel functional chemicals LLC. Fyrol FR-2 Material Safety Data Sheet, MSDS No. 16-084513, Printed 12/10/2003.
- Anderson, BT. 1990. Amgard TDCP: Acute inhalation toxicity study in rats. Inveresk Research International (Report No.7293). Cited in WHO (1998) as Anderson (199b).
- Aston, LS; Noda J; Reece CA. 1996. Organophosphate flame retardants in needles of *Pinus ponderosa* in the Sierra Nevada foothills. *Bull. Environ. Contam. Toxicol.* 57: 859-866.
- Bio/Dynamics, Inc. 1980. A two-year oral toxicity/carcinogenicity study of Fyrol FR-2 in rats (Volume I-IV). TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911. [Published as Freudenthal and Henrich, 2000]
- Bio/Dynamics, Inc. 1981. A two-year oral toxicity/carcinogenicity study of Fyrol FR-2 in rats (Volume V). TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911-1. [Published as Freudenthal and Henrich, 2000]
- Bloom, SE. 1984. Sister chromatid exchange studies in the chick embryo and neonate: actions of mutagens in a developing system. *Basic Life Sci.* 29B: 509-533.
- Brusick, DJ; Jagannath, DR. 1977. Sex-linked recessive lethal assay in *Drosophila* evaluation of Fyrol FR-2: Final report. Report T-6355. Stauffer Chemical Company. Cited in WHO, 1998. See Litton Bionetics (1976a).

Brusick, D; Matheson, D; Jagannath, DR; et al. 1979. A comparison of the genotoxic properties of tris(2,3-dibromopropyl)phosphate and tris(1,3-dichloro-2-propyl)phosphate in a battery of short-term bioassays. *J. Environ. Pathol. Toxicol.* 3: 207-226.

Budavari, S. (ed.). 2001. *Fyrol FR-2. The Merck index - An encyclopedia of chemicals, drugs, and biologicals.* 13th ed. Whitehouse Station, NJ: Merck and Co., Inc.

Bullock, CH; Kamienski, FX. 1972. Stauffer Chemical Company, Western Research Center Report T-4055. Cited in WHO (1998). See Stauffer (1972a).

CERI. 1999. Chemicals Inspection and Research Institute, Japan. Available on-line at www.cerij.or.jp/ceri_en/index_e4.shtml. Accessed July 2004.

Chemicals Inspection and Testing Institute. 1992. *Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology and Information Center.* ISBN 4-89074-101-1.

Choudhry, CG; Hutzinger, O. 1982. *Residue Rev.* 84: 113-161.

Cuthbert, JA. 1989a. Tolgard TDCP MK1: Acute oral toxicity (LD50) test in rats. Report No. 5689. Inveresk Research International. Cited in WHO (1998).

Cuthbert, JA. 1989b. Tolgard TDCP MK1: Acute dermal toxicity (LD50) test in rats. Report No. 5690. Inveresk Research International. Cited in WHO (1998).

Cuthbert, JA. 1989c. Tolgard TDCP MK1: Acute dermal irritation test in rabbits. Report No. 5691. Inveresk Research International. Cited in WHO (1998).

Cuthbert, JA; Jackson, D. 1990. Tolgard TDCP MK1: Acute eye irritation test in rabbits. Report No. 7200. Inveresk Research International. Cited in WHO (1998) as Cuthbert and Jackson (1990a).

Eldefrawi, AT; Mansour, NA; Brattsten, LB; et al. 1977. Further toxicological studies with commercial and candidate flame retardant chemicals. Part II. *Bull. Environ. Contam. Toxicol.* 17: 720-726.

EPIWIN. 2000. v. 3.11. Downloadable at <http://www.epa.gov/oppt/exposure/docs/episuitedi.htm>. ©2000 U.S. Environmental Protection Agency.

Freudenthal, RI; Henrich, RT. 2000. Chronic toxicity and carcinogenic potential of Tris(1,3-dichloro-2-propyl) phosphate in Sprague-Dawley rat. *Int. J. Toxicol.* 19: 119-125. [see also Bio/Dynamics, 1980]

Gold, MD; Blum, A; Ames, BN. 1978. Another flame retardant, tris-(1,3-dichloro-2-propyl)-phosphate, and its expected metabolites are mutagens. *Science*. 200: 785-787.

Hazleton (Hazleton Laboratories America, Inc.). 1978. Teratology study in rats. FR-2 (Fyrol). (Final report). TSCA 8e submission by Stauffer Chemical Corporation (1981) Toxicological reports on Fyrol FR-2 (Volume I, Report T-6331). OTS0204911 (fiches 3-4 of 32). (Cited in NRC, 2000 as Stauffer Chem. Co., 1977-1978).

Hollifield, HC. 1979. Rapid nephelometric estimate of water solubility of highly insoluble organic chemicals of environmental interest. *Bull. Environ. Contam. Toxicol.* 23: 579-586.

HSDB. 2003. Tris(1,3-dichloro-2-propyl) phosphate. Hazardous Substances Data Bank. The National Library of Medicine. Available on-line at <http://toxnet.nlm.nih.gov/cgi-bin/sis/>. Accessed July 2004.

IPCS. 1998. Environmental Health Criteria, Vol. 209. Flame retardants. Tris(chloropropyl) phosphate and tris(2-chloroethyl) phosphate. International Programme on Chemical Safety. Geneva, World Health Organization.

Kamata, E; Naito, K; Nakaji, Y; et al. 1989. Acute and subacute toxicity studies of tris (1,3-dichloro-2-propyl) phosphate on mice. *Bull. Natl. Inst. Hyg. Sci. (Tokyo)* 107: 36-43. [In Japanese with tables and abstract in English]

Lewis, R. 2000. Fyrol FR 2. Sax's dangerous properties of industrial materials. 10th Ed. New York, NY: John Wiley & Sons, Inc., p732.

Litton Bionetics, Inc. 1976. Mutagenicity evaluation of Fyrol FR-2 (Final Report): Sex-linked *Drosophila*.. Report T-6355. TSCA 8e submission by Stauffer Chemical Corp., 1981, OTS0204911 (fiche 5).

Litton Bionetics, Inc. 1977. Mutagenicity evaluation of Fyrol FR-2 (Final Report). Reports T-6385: Mouse lymphoma multiple endpoints: mutagenicity, clastogenicity, sister chromatid exchange. TSCA 8e submission by Stauffer Chemical Corp., 1981, OTS0204911 (fiche 8).

Litton Bionetics, Inc. 1978. Mutagenicity evaluation of Fyrol FR-2 (Final Report): Mouse bone marrow cytogenetic analysis. Report T-6354. TSCA 8e submission by Stauffer Chemical Corp., 1981, OTS0204911 (fiche 6-7).

Luster, MI; Dean, JH; Boorman, GA; et al. 1981. The effects of orthophenylphenol, tris(2,3-dichloropropyl) phosphate, and cyclophosphamide on the immune system and host susceptibility of mice following subchronic exposure. *Toxicol. Appl. Pharmacol.* 58: 252-261. [Note TDCPP is misnamed in this paper]

Majeska, JB; Matheson, DW. 1983. Quantitative estimate of mutagenicity of tris-(1,3-dichloro-2-propyl) phosphate (TCPP) and its possible metabolites in Salmonella. Environ. Mutagen. 5: 478-479.

Mortelmans, K; Haworth, S; Lawlor, T; et al. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ. Mutagen. 8(Suppl. 7): 1-119.

Nakamura, A; Tateno, N; Kojima, S; et al. 1979. Mutagenicity of halogenated alkanols and their phosphoric acid esters for Salmonella typhimurium. Mutat. Res. 66: 373-380.

NICNAS. 2001. Triphosphates. Priority Existing Chemical Assessment Report No. 17. National Industrial Chemicals Notification and Assessment Scheme. June 2001. Commonwealth of Australia, 2000.

NRC (National Research Council). 2000. Tris(1,3-dichloropropyl-2) phosphate. In: toxicological risks of selected flame retardant chemicals. National Academy Press: Washington, D.C. p358-386.

Prival, MJ; McCoy, EC; Gutter, B; et al. 1977. Tris(2,3-dibromopropyl) phosphate: mutagenicity of a widely used flame retardant. Science. 195: 76-78.

SafePharm. 1993a. Acute toxicity to rainbow trout (Amgard TDCP). Derby, England, SafePharm Laboratories (Unpublished report No. 071/272). Cited in IPCS, 1998.

SafePharm. 1993b. Acute toxicity to Daphnia magna (Amgard TDCP). Derby, England, SafePharm Laboratories (Unpublished report No. 071/271). Cited in IPCS, 1998.

SafePharm. 1994. Assessment of the algistatic effect of Amgard TDCP. Derby, England, SafePharm Laboratories (Unpublished report No. 071/273). Cited in IPCS, 1998.

SafePharm. 1996. Acute toxicity to earthworms (Amgard TMCP). Derby, England, SafePharm Laboratories (Unpublished report No. 071/458). Cited in IPCS, 1998.

Sasaki, K; Takeda, M; Uchiyama, M. 1981. Toxicity, absorption, and elimination of phosphoric acid triesters by killifish and goldfish. Bull. Environ. Contam. Toxicol. 27: 775-782.

Sasaki, K; Suzuki, T; Takeda, M. 1982. Bioconcentration and excretion of phosphoric acid triesters by killifish (*Oryzeas latipes*). Bull. Environ. Contam. Toxicol. 28: 752-759.

Soederlund, EJ; Dybing, E; Holme, JA; et al. 1985. Comparative genotoxicity and nephrotoxicity studies of the two halogenated flame retardants tris(1,3-dichloro-2-propyl) phosphate and tris(2,3-dibromopropyl)phosphate. Acta Pharmacol. Toxicol. 56: 20-29.

SRC. 2004. PHYSPROP (Physical Properties Data Base). Tris(1,3-dichloro-2-propyl) phosphate. Syracuse Research Corporation. Available online at <http://www.syrres.com/esc/physprop.htm>. Accessed July 2004.

Stauffer (Stauffer Chemical Co.). 1972a. Toxicology reports on Fyrol FR-2. Vol I of II: Demyelination study in hens. Report T-4055. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1972b. Toxicology reports on Fyrol FR-2. Vol I of II: Cholinesterase inhibition in male rats. Report T-4055-1. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1972c. Toxicology reports on Fyrol FR-2. Vol I of II: 4-hour skin irritation, eye irritation. Report T-4055-4. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1972d. Toxicology reports on Fyrol FR-2. Vol I of II: Acute oral toxicity in male rats. Report T-4100-2. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1973a. Toxicology reports on Fyrol FR-2. Vol I of II: Acute Dermal toxicity in rabbits. Report T-4287. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1973b. Toxicology reports on Fyrol FR-2. Vol I of II: Acute inhalation toxicity. Report T-4782. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1978. Toxicology reports on Fyrol FR-2. Vol I of II: Summary of in vitro delayed neurotoxicity evaluation. Report T-6303. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1979. Toxicology reports on Fyrol FR-2. Vol I of II: 24-hour skin irritation, eye irritation. Report T-6773. TSCA 8e submission by Stauffer Chemical Company (1981), OTS0204911 (fiche 3).

Stauffer (Stauffer Chemical Co.). 1981. Toxicology reports on Fyrol FR-2 (volume I-II with attachments and cover letter dated 020381. Stauffer Western Research Center. EPA Doc. No 8EHQ-9-0281-0401 Fiche No. OTS0204911.

Tanaka, S; Nakaura, S, Kawashima, K; et al. 1981. Effect of oral administration of tris(1,3-dichloroisopropyl)phosphate to pregnant rats on prenatal and postnatal developments. Eisei Shikenjo Hokoku 99: 50-55. [In Japanese with abstract and tables in English]

Thomas, MB; Collier, TA. 1985. Tolgard T.D.C.P. LV: OECD 474 Micronucleus study in the mouse. Experiment No. 164/8507. Safepharm Laboratories. Cited in WHO (1998).

WHO. 1998. International Programme on Chemical Safety (IPCS), Environmental Health Criteria 209, Flame retardants: tris(chloropropyl)phosphate and tris(2-chloroethyl)phosphate. World Health Organisation. Available online at www.inchem.org/documetns/ehc/ehc/ehc209.htm. Accessed July 2004.

Wilczynski, SI; Killinger, JM; Zwicker, GM; et al. 1983. Fyrol FR-2 fertility study in male rabbits. Toxicologist. 3: 22 (abstract).